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TELEFAX

To: Examiner Susannah Lee
US Patent & Trademark Office
Art Unit 1626

From:

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TOTAL PAGES: 9 including this cover sheet
Fax Number: 571-273-8300
February 9, 2005

Re: Patent Application 10/808,889
Filing Date: 3/25/2004
Attorney docket number: ST01027 US CNT

Dear Examiner Lee:

Attached is the International Preliminary Examination Report that you requested via a voice mail message that I received February 8, 2005.

Please contact me if there should be further questions or additional information that you require.

Best regards.

Lawrence L. Martin
Reg No. 46,902

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US S/N 10/808,889
Filed: 3/25/2004

AVENTIS US PAT DEPT

NO. 2107 P. 2

Attorney Docket: ST01027 US CNT **PATENT COOPERATION TREATY**

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Le Pennec, Magali
AVENTIS PHARMA S.A.
Patent Department
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F-92165 Antony Cedex
FRANCE

DIRECTION BREVETS

27 OCT 2003

PATENT DEPARTMENT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

23.10.2003

Applicant's or agent's file reference
ST 01027

IMPORTANT NOTIFICATION

International application No.
PCT/EP02/11353

International filing date (day/month/year)
26.09.2002

Priority date (day/month/year)
26.09.2001

Applicant
AVENTIS PHARMA S.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



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Authorized Officer

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US S/N 10/808,889



Filed: 3/25/2004

Attorney Docket: ST01027 US CNT

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ST 01027	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEPA416)	
International application No. PCT/EP02/11353	International filing date (day/month/year) 26.09.2002	Priority date (day/month/year) 26.09.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/4184		
Applicant AVENTIS PHARMA S.A.		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 4 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 507 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>		
Date of submission of the demand 25.03.2003	Date of completion of this report 23.10.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax: +49 89 2399 - 4485	Authorized Officer Béron, L Telephone No. +49 89 2399-7078 	

US S/N 10/808,889

Filed: 3/25/2004

Attorney Docket: ST01027 US CNT

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/EP02/11353****I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*)

Description, Pages

1-143 as originally filed

Claims, Numbers

1-9 received on 15.09.2003 with letter of 11.09.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/EP02/11353****V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	9
	No: Claims	1-8
Inventive step (IS)	Yes: Claims	9
	No: Claims	1-8
Industrial applicability (IA)	Yes: Claims	1-9
	No: Claims	

2. Citations and explanations**see separate sheet**

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP02/11353

RE ITEM V**RECEIVED
CENTRAL FAX CENTER****FEB 09 2005****1 Prior art**

D1: WO 0041669

D2: EP 0115 039

D3: DE 2541752

2 Novelty (Article 33(1) and (2) PCT)

The present compounds overlap with the compounds disclosed in D1 (see claim 1, formula I), D2 (see claim 1, formula I) and D3 (see claim 1, formula 1). No technical teaching is apparent in the present compounds which would render them novel. Accordingly, D1-D3 are prejudicial to the novelty of the present application.

It is noted that the disclaimer introduced in the amended set of claims dated 15.09.2003 does not disclaim the whole overlapping area. Overlap still remains for example when A is substituted by aryl and heteroaryl groups (see D1, claim 2 and description on page 3), when A is substituted by a tetrafluoroethoxy group (see D2, claim 1), when A is substituted by a CF₃ group (see D3, claim 1) etc.

3 Inventive step (Article 33(1) and (3) PCT)

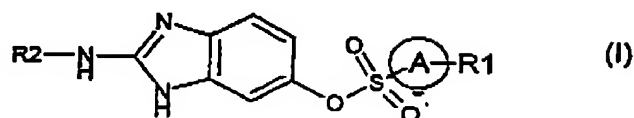
The technical problem underlying the present application lies in the provision of inhibitors of cyclin-dependent kinases (CDKs) useful for the treatment of cancer. D1 which represents the closest prior art discloses structurally related benzimidazoles (see also item 2). However, said benzimidazoles were used as vascular damaging agents (see page 1, line 1-3). The skilled person would therefore not have considered the present compounds as solution of the above-stated problem. Accordingly, an inventive step can be acknowledged for the present subject-matter delimited from D1-D3.

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CLAIMS

1 - Compounds of formula (I)



- wherein A is an aryl or heteroaryl entity
- wherein R₁ is selected from one or more similar groups selected from:
 - alkyl, eventually substituted by an alkoxy, heteroalkyl, aryl, acyl, acyl derivatives, halogen
 - alkoxy eventually substituted by an alkyl, heteroalkyl, aryl, heteroaryl, alkoxyalkyl, hydroxyalkyl amide or a perfluoroalkoxy group or an alkylthio eventually substituted by an amide or a perfluoroalkylthio
 - aryl or heteroaryl eventually substituted by one or more alkyl group, alkoxy group, nitro group, cyano group, acyl derivative, perfluoroalkoxy group, perfluoroalkyl group, heteroaryl group, aryloxy group
 - halogen
 - 4 NH₂
 - 4 NH alkyl or cycloalkyl eventually substituted with an an acyl, an acyl derivative, an hydroxy, an amino, alkoxy, heterocyclyl or aryl group
 - 4 N imidazolyl
 - 3 SO₂ Me when A is phenyl
- wherein R₂ is selected from the group consisting of
 - CO-alkyl eventually substituted by amino, acid, acid derivative, alkoxy, aryl or OH groups

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- CO-aralkyl eventually substituted by alkoxy, halogeno, amino, acid or acid derivatives
 - CO-aryl eventually substituted
 - CO-alkoxy eventually substituted by aryl
 - 5 - CO-amino, CO-NHR₃, CO-NR₃R₄ wherein R₃ and R₄ are selected independently from hydrogen, alkyl, hydroxyalkyl, alkoxyalkyl, fluoroalkyl, alkenyl, heteroalkyl, alkylheteroalkyl, aryl, aralkyl or together form an alkylene chain including eventually one to 4 heteroatoms
 - 10 - aryl or aralkyl eventually substituted by heterocycloalkyl, alkyl, aryl, alkoxy, amino, fluoroalkyl, acyl derivatives, halogen
- or a pharmaceutically acceptable salt or a prodrug
provided that R₁ cannot be halogen, alkyl or alkoxy when R₂ is -CO-alkoxy.
- 2 - Compounds according to claim 1 wherein A is selected from phenyl,
15 thiophen, isoxazole, oxazole, pyrazole, furane, pyridine.
- 3 - Compounds according to claim 2 wherein A is phenyl.
- 4 - Compounds according to claim 1 wherein the aryl, aralkyl, heteroaryl or heteroarylalkyl groups are eventually substituted with one or more similar or different
20 groups selected from halogen, alkoxy, alkyl, hydroxyalkyl, alkylthio, amino, mono or dialkylamino, heterocyclamino, arylamino, heteroarylamino, heteroaryl, nitro, heterocycloalkyl, perfluoroalkyl, perfluoroalkoxy, perfluoroalkylthio, acyl derivatives.
- 5 - Compounds according to claim 1 wherein the alkyl or alkylene substituents are substituted with one or more amino, aminoalkyl, aminoalkylamino, hydroxy, alkoxy, hydroxyalkoxy, acyl, acyl derivatives, alkyl, heteroalkyl, arylalkyl, arylamino, aryloxy,
25 or aryl groups.
- 6 - Compounds according to claim 1 wherein the alkoxy or alkylthio substituents are substituted with one or more amino, acyl, acyl derivatives, alkyl, arylalkyl or aryl groups.

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7 - Compounds according to claim 1 wherein the acyl groups or acyl derivatives groups include carboxylic acids and sulfonic acids or derivatives.

8 - Compounds according to claim 5 wherein the acid derivatives include alkyl esters and carbamoyl esters.

5 9 - Use of the compounds of formula (I) for treating cancer diseases.